ORIGINAL ARTICLE MYCOLOGY

# A retrospective series of gut aspergillosis in haematology patients

**E. Kazan[1], J. Maertens[2], R. Herbrecht[3], M. Weisser[4], B. Gachot[5], A. Vekhoff[6], D. Caillot[7], E. Raffoux[8], T. Fagot[9], O. Reman[10], F. Isnard[11], A. Thiebaut[12], S. Bretagne[13] and C. Cordonnier[1]**

1) *Haematology Department, Henri Mondor Teaching Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP) and Paris 12 University, Créteil, France,* 2) *Haematology Department, Acute Leukaemia and Stem Cell Transplantation Unit, UZ Gasthuisberg, Leuven, Belgium,* 3) *Oncology and Haematology Department, Hôpital de Hautepierre, Strasbourg, France,* 4) *Division of Infectious Diseases and Hospital Epidemiology, University Hospital, Basel, Switzerland,* 5) *Pole Microbiologie et Maladies Infectieuses, Institut Gustave Roussy, Villejuif,* 6) *Haematology Department, Hôtel Dieu Teaching Hospital, AP-HP, Paris,* 7) *IFM, University Hospital Bocage, Dijon,* 8) *Haematology Department, EA 3518, Université Paris VII, Hôpital Saint Louis, AP-HP, Paris,* 9) *Haematology Department, Hôpital des Armées, Clamart,* 10) *Haematology Department, University Hospital, Caen,* 11) *Haematology Department, Hopital Saint-Antoine, AP-HP, Paris,* 12) *Haematology Department, University Hospital, Grenoble and* 13) *Parasitology-Mycology Department, Henri Mondor Teaching Hospital, AP-HP and Paris 12 University, Créteil, France*

## Abstract

Gut invasive aspergillosis is an extremely rare infection in immunocompromised patients. The goal of this retrospective multicentre study is to report on cases of gut aspergillosis in haematology patients, including clinical presentation, risk factors, and outcome. Twenty-one patients from nine centres were identified. Eight had isolated gut aspergillosis, with no evidence of other infected sites, and 13 had disseminated aspergillosis. Thirteen patients had acute leukaemia. Nine were allogeneic stem cell transplant recipients. Clinical symptoms and imaging were poorly specific. The galactomannan antigenaemia test result was positive in 16/25 (64%) patients, including in four of the eight cases of isolated gut aspergillosis. Five of 21 patients had a dietary regimen rich in spices, suggesting that, in these cases, food could have been the source of gut colonization, and then of a primary gut *Aspergillus* lesion. The diagnosis was made post-mortem in six patients. The mortality rate in the remaining patients at 12 weeks was 7/15 (47%). Gut aspergillosis is probably misdiagnosed and underestimated in haematology patients, owing to the poor specificity of symptoms and imaging. Patients with a persistently positive galactomannan antigenaemia finding that is unexplained by respiratory lesions should be suspected of having gut aspergillosis in the presence of abdominal symptoms, and be quickly investigated. In the absence of severe abdominal complications leading to surgery and resection of the lesions, the optimal treatment is not yet defined.

**Keywords:** Acute leukaemia, gut infection, invasive aspergillosis, stem cell transplantation
**Original Submission:** 12 April 2010; **Revised Submission:** 19 May 2010; **Accepted:** 24 June 2010
Editor: E. Roilides
**Article published online:** 15 July 2010
*Clin Microbiol Infect* 2011; **17:** 588–594
10.1111/j.1469-0691.2010.03310.x

**Corresponding authors:** C. Cordonnier, Haematology Department, Henri Mondor University Hospital, 94000 Créteil, France
**E-mail: carlcord@club-internet.fr**

E. Kazan, Haematology Department, Henri Mondor University Hospital, 94000 Créteil, France
**E-mail: ekazan75@hotmail.com**

The preliminary results of this study were presented as a poster at the American Society of Hematology Meeting, New Orleans, Louisiana, December 2009.

## Introduction

Invasive aspergillosis (IA) is a life-threatening infection in immunocompromised patients, mainly in acute leukaemia and allogeneic haematopoietic stem cell transplant (HSCT) recipients [1]. The frequency of IA has obviously increased during the last 20 years, as a consequence of the use of more effective, but also more toxic, chemotherapy and immunosuppressing regimens, besides the growing number of HSCT cases [1].

Aspergillosis mainly involves the lower respiratory tract and the sinuses. Other sites of infection are rarely observed, except in case of dissemination [3–6].

Gut aspergillosis, either isolated or in the setting of disseminated infection, has been occasionally reported in the literature [2]. The largest report of digestive fungal infection—*Aspergillus* or *Candida*—was an autopsy series of patients with haematological diseases [3], whereas the first case in a living patient was reported in 1985 after a right colostomy in a haematology patient [4]. In a review of two personal cases and eight cases of the literature, Eggiman *et al.*

[5] have pointed out some characteristic features of IA of the digestive tract, suggesting that the gut could be a portal of entry for *Aspergillus* in immunocompromised patients.

Following three cases over 8 years in the haematology department of Henri Mondor Hospital, we were interested in collecting data from other centres. The goal of this retrospective multicentre study was to report on the clinical presentation, risk factors and outcome of gut aspergillosis in haematology patients.

## Methods

This was a multicentre retrospective study. In April 2009, we sent a questionnaire to 13 haematology centres in France and to four centres in Belgium and Switzerland. Nine of these 17 centres had seen at least one case of gut aspergillosis over the last 13 years and agreed to participate. The study design was approved by the Comité de Protection des Personnes Ile de France IX.

We elaborated a questionnaire to collect data anonymously. It was filled in from the medical chart, either by the local investigator, or by the first author. Inclusion criteria were [1] haematological disease, including aplastic anaemia, and [2] proven gut aspergillosis, diagnosed either pre-mortem or post-mortem. Isolated liver or spleen localizations were excluded, as well as cases documented only by PCR on tissue, without histological findings of mould infection.

As the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) does not propose any criteria for a diagnosis of probable gut aspergillosis [6], we collected data only from patients with proven disease, documented through mucosal alteration and tissue invasion in a biopsy specimen (obtained by endoscopy or surgery) or by autopsy. Only patients with tissue culture-proven aspergillosis, or with gut biopsy specimens showing tissue invasion by filamentous fungi suggestive of *Aspergillus* and a positive serum galactomannan (GM) antigenaemia test finding (ratio of ≥0.5) were selected. The criteria of Segal *et al.* [7] were used to assess the response to treatment at 12 weeks after the diagnosis. Patients were considered to have an isolated gut aspergillosis if the available investigations performed did not show any other focus consistent with probable or definite (biopsy-proven) aspergillosis according to the EORTC/MSG criteria [6]. Patients with at least one other lesion outside the gut were considered to have disseminated aspergillosis.

### Patients

Twenty-one patients were included. One patient (patient 3) has been previously reported [8]. Fifteen patients were from France, two from Switzerland, and four from Belgium. The mean age of patients was 48 years (range: 18–70 years). There were 12 females and nine males. The underlying disease was acute leukaemia in 13, acceleration of chronic myeloid leukaemia in two, lymphoma in two, myeloma in three, and myelodysplastic syndrome in one. Nine patients had received an allogeneic HSCT, five from a human leukocyte antigen-identical donor, three from an unrelated donor, and one from a cord blood. The conditioning regimens were classified according to the European Group for Blood and Marrow Transplantation recommendations, as either a standard or a reduced-intensity conditioning regimen [9]. Four HSCT patients were transplanted with a standard regimen, and five with a reduced-intensity conditioning regimen. Thirteen of 21 patients (57%) were neutropenic at the time of diagnosis. Eleven patients had received a recent course of high-dose cytosine arabinoside. Twelve patients were receiving ($n$ = 6) or had received ($n$ = 6) steroids within the last 60 days. The characteristics of the patients are presented in Table 1.

## Results

Of the 21 patients, 14 were febrile at the time of diagnosis. The clinical presentation included diarrhoea in ten, abdominal pain in 17, gut haemorrhage in seven, intestinal occlusion in six, and perforation in one. Imaging of the abdomen—echography, computed tomography (CT) and/or magnetic resonance imaging—was performed in 14 cases: two findings were normal, and the others were suggestive of gut abnormalities (isolated or diffuse oedema and thickening of intestinal wall), or only intestinal dilatation (Fig. 1).

Twenty patients had, concomitantly with the diagnosis of gut aspergillosis, a chest CT scan, and 14 had a CT scan or magnetic resonance imaging scan of the head. Eight patients had an isolated gut lesion (patients 1–8), and 13 had disseminated disease (patients 9–21).

The gut symptoms, which were poorly specific, mostly led to endoscopy when lesions were thought to be accessible; only two of 17 patients with lower gut lesions (small bowel, $n$ = 9; colon or rectum, $n$ = 8) were diagnosed by endoscopy; the diagnosis was performed by endoscopy in five of nine patients with upper gut lesions (oesophagus, $n$ = 2; stomach, $n$ = 3; duodenum, $n$ = 4). All patients had a gut biopsy specimen that was positive for the presence of invasive filamentous fungi (Fig. 2a,b) and additionally showed ulcerative ($n$ = 3), perforative ($n$ = 3) or necrotic lesions secondary to angio-invasive aspergillus embolism ($n$ = 6). In one case, histology showed a pattern of necrotizing

**TABLE 1. Clinical characteristics of the 21 patients with gut aspergillosis**

| Patient no. | Age (years)/ sex | Underlying disease | Treatment phase (type of conditioning if HSCT) | Neutropenia <500/μL at diagnosis | Site of gut infection | Other sites infected at diagnosis | Diagnosis procedure | Mycological culture of the gut biopsy specimen | GM antigenaemia serum test at time of diagnosis (index) | Gut surgery | Outcome at 12 weeks after diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 56/F | AML first phase | Induction | + | Duodenum | No | Endoscopy | Positive | Not available | Yes | Survived, complete response |
| 2 | 62/F | AML in CR | Cord blood HSCT day 77 (RIC) | – | Colon | No | Endoscopy | Positive | Negative | No | Survived, response not evaluated |
| 3 | 54/F | AML first phase | Induction | + | Small bowel | No | Laparotomy | Not done | 6.4 | Yes | Died in the operating theatre |
| 4 | 24/F | Accelerated CML | Induction | + | Colon | No | Laparotomy | Not done | Negative | Yes | Death, at 57 days after diagnosis |
| 5 | 19/M | AML first phase | Induction | + | Appendix | No | Laparotomy | Negative | 0.6 | Yes | Survived, complete response |
| 6 | 58/F | ALL in CR | Consolidation | – | Colon | No | Endoscopy | Positive | 4.2 | No | Survived, complete response |
| 7 | 51/M | Multiple myeloma | HLA-identical HSCT day 303 (RIC) | – | Stomach | No | Endoscopy | Positive | Negative | Yes | Death, at 17 days after diagnosis |
| 8 | 70/F | AML in RC | Consolidation | + | Duodenum | No | Laparotomy | Negative | 0.9 | Yes | Survived, complete response |
| 9 | 62/F | Multiple myeloma | Unrelated HSCT day 105 (standard) | + | Small bowel | Lung (probable) | Laparotomy | Not done | 3.6 | Yes | Death, at 16 days after diagnosis |
| 10 | 52/M | Lymphoma first phase | Induction | + | Small bowel | Lung (probable) | Laparotomy | Positive | 9.9 | Yes | Death, at 20 days after diagnosis |
| 11 | 23/M | AML in CR | HLA-identical HSCT day 62 (standard) | – | Colon | Lung (proven), CNS | Autopsy | Not done | 1 | No | – |
| 12 | 44/F | Refractory lymphoma | R-DHAP | – | Stomach | Lung (proven), CNS | Endoscopy | Positive | 2 | No | Survived, partial response |
| 13 | 64/M | AML first phase | Induction | + | Small bowel | Lung (possible) | Laparotomy | Positive | 4.6 | Yes | Survived, complete response |
| 14 | 54/F | AML relapse | Salvage | + | Small bowel | Lung (probable) | Laparotomy | Not done | 7.7 | Yes | Survived, complete response |
| 15 | 55/F | AML relapse | Salvage | + | Small bowel | Lung (probable) | Laparotomy | Not done | Negative | Yes | Death, at 19 days after diagnosis |
| 16 | 38/M | Accelerated CML | HLA-identical HSCT day 137 (Standard) | – | Rectum | Lung (proven) CNS, liver, skin, kidney, heart, spleen | Autopsy | Positive | 0.6 | No | – |
| 17 | 40/F | AML relapse | HLA-identical HSCT day 8 (RIC) | + | Small bowel | Lung (proven) | Autopsy | Positive | 0.5 | No | – |
| 18 | 65/F | MDS in RC | Unrelated HSCT day 110 (RIC) | + | Duodenum | Lung (proven) | Autopsy | Not done | 1.4 | No | – |
| 19 | 18/M | ALL in CR | HLA-identical HSCT day 117 (standard) | – | Stomach | Lung (proven), pancreas, pericardium, adrenal gland | Autopsy | Positive | 6 | No | – |
| 20 | 54/M | Multiple myeloma | Unrelated HSCT day 54 (RIC) | – | Duodenum | Lung (probable) | Endoscopy | Not done | 0.5 | No | Death, at 38 days after diagnosis |
| 21 | 55/M | ALL, first phase | Induction | + | Small bowel | Liver, CNS | Laparotomy | Positive | 4.5 | Yes | Death, at 79 days after diagnosis |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; CNS, central nervous system; CR, complete remission; F, female; GM, galactomannan; HLA, human leukocyte antigen; HSCT, haematopoietic allogeneic stem cell transplantation; M, male; MDS, myelodysplastic syndrome; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; RIC, reduced-intensity conditioning.

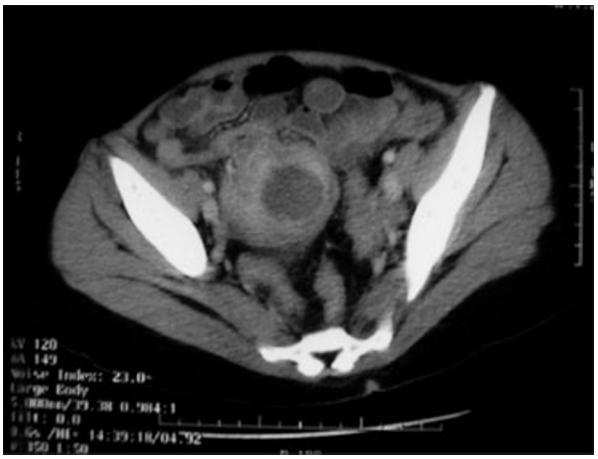

**FIG. 1.** Abdominal computed tomography scan of patient 4 showing a heterogeneous mass containing liquid in the wall of the colon.

pseudotumour. Two patients had extensive inflammatory, ulcerative lesions of the stomach and duodenum. Culture of the tissue was performed in 13 cases, and gave positive findings in 11, yielding *Aspergillus fumigatus* ($n$ = 10) or *Aspergillus flavus* ($n$ = 1). GM antigenaemia testing was performed in 20 cases, and gave a positive finding at least once in 16 patients (median index of 3.3), including eight patients of the 11 with a positive culture. Five patients (patients 1, 6, 9, 14, and 21) had transient positivity of stool cultures for *Aspergillus*, but this was not considered to be a diagnostic criterion. In three of these five patients, both gut biopsy and stools grew *A. fumigatus*. Six patients were diagnosed with gut aspergillosis only after death, in four of them after a prolonged history of unexplained gut symptoms: five at autopsy, and in one case after the patient had died during surgery (patient 3). All of these six patients had received empirical antifungal therapy with deoxycholate amphotericin B or caspofungin for 1–10 days before they died.

All patients diagnosed before death received antifungal agents, mostly voriconazole ($n$ = 8) or liposomal amphotericin B ($n$ = 4), for first-line treatment, and for 2–7 months after diagnosis. Four patients received combinations of antifungals at some point in their treatment. Twelve patients were operated on, ten for both diagnosis and therapeutic purposes, and two for fungal resection when the aetiologic diagnosis was already known before surgery. Six of them died. Nine of these 12 patients were operated on while they were neutropenic.

According to the criteria of Segal *et al.* [7], excluding the six patients diagnosed post-mortem, eight of the 15 remaining patients (53%) survived at 12 weeks; six had a complete response, one had partial response, and one was not evaluable. Seven of the 12 patients who underwent surgery died, as compared with six of the nine patients who did not. Of

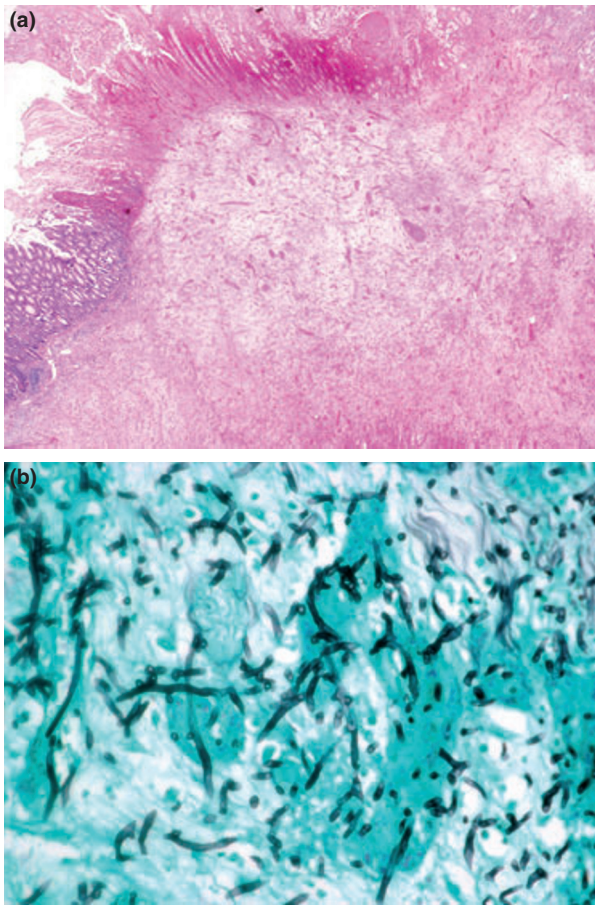


**FIG. 2.** (a) Haematoxylin and eosin-stained histological section (×1.25 original magnification) obtained after right hemi-colonectomy of patient 4, showing an abscess with mucosal disruption. Numerous hyphae compatible with *Aspergillus* were seen in the abscess with additional staining and higher magnification. (b) Intestinal section obtained after right hemi-colonectomy of patient 4, showing *Aspergillus* hyphae (Gomori–Grocott staining; magnification ×40).

the eight patients with isolated gut aspergillosis, excluding patient 4, who died in the operating theatre, five underwent surgery, and three of these five died later. Ten of the 13 patients with disseminated aspergillosis died at 12 weeks; one additional patient (patient 5) who was alive at 12 weeks died 4 weeks later.

As the three Creteil patients were from the French Caribbean, Commores, and Africa, and we never saw any case in Caucasian patients, we looked at the ethnic and geographical origin of the patients from other centres, hypothesizing that a non-European origin could be associated with special food, rich in spices [10]. Three patients (patients 3, 4, and 5) were either from Africa, the Pacific Ocean or the Antilles; one French woman (patient15) had eaten a purely African diet for 10 years; and patient 2 had been living in Tahiti for

2 years before the diagnosis of gut IA. Four of these five patients had isolated gut lesions.

## Discussion

The gut is a very rare location of IA in the literature. In the exhaustive review by Eggiman *et al.* [5], it accounted for 5.5% of 1538 cases of aspergillosis. Most cases were observed in disseminated disease; isolated gut aspergillosis was very exceptional (0.8%) [5]. However, considering the higher incidence rate in autopsy series [2,11–14], it is likely that the diagnosis is underestimated before death, owing to the poor specificity of the clinical symptoms and imaging. This is also supported by the fact that five of our 21 patients were diagnosed only at autopsy.

Our series is the largest series of gut aspergillosis so far reported. The retrospective design of this study precluded the possibility of systematic investigative procedures and treatments. However, some main findings emerge from our series.

First, we were unable to find any characteristic clinical or imaging features of gut aspergillosis. As most gut symptoms result from necrotic lesions, obstruction or haemorrhage, it is likely that there is no characteristic clinical presentation or imaging for such lesions. Most of the symptoms would have oriented the clinician to a bacterial complication with typhlitis, or neutropenic enterocolitis that may have preceded the gut lesions and favoured yeast colonization on an altered mucosa, through mucositis favoured by high-dose aracytine or gut graft-versus-host disease. Many patients may therefore have been given antibacterials and gut aspiration without any other treatment. However, in two cases, the abdominal CT scan showed images of masses or abscesses (Fig. 1) leading to surgery on the assumption of a bacterial or tumoral lesion. In other cases, the occurrence of an acute, severe complication, such as occlusion, or peritonitis, could have driven the decision to operate in these very critical patients. In our series, the lower gastrointestinal tract (small bowel, colon, and rectum) appears to be more frequently involved (17/21) than the upper gastrointestinal tract (oesophagus and stomach) (9/21), although five of our patients had concomitant upper and lower involvement, but this may be biased by the absence of a common diagnostic strategy. Some of these localizations, especially of the small bowel, are usually not accessible by endoscopy; surgery is usually needed for early diagnosis.

Second, gut aspergillosis can occur either in an isolated site or, more frequently, in the setting of a disseminated aspergillosis. The prognosis in the setting of disseminated aspergillosis is extremely poor and consistent with previous series reporting patients with multiple localizations of infection [14,15]. Because autopsy has not been systematically performed, we cannot definitely exclude other concomitant localizations in the patients who were considered to have 'isolated' gut lesions. However, all but one of the patients had a chest CT scan performed, which did not indicate any lung lesion**.** This small group of eight patients with isolated gut aspergillosis suggests that the hypothesis of a digestive (instead of respiratory) portal of entry is reasonable. It suggests either recent ingestion of food that is highly contaminated with *Aspergillus*, or chronic low-burden ingestion with asymptomatic gut colonization, which becomes clinically manifest in conditions of immunosuppression and mucositis. These cases could be real cases of 'primary' gut aspergillosis, where the gut is the portal of entry and there are local invasive lesions, but the infection does not disseminate. This hypothesis is supported by a historical publication that reported contamination of food with *Aspergillus* spp. from pepper in the setting of an *Aspergillus* outbreak in a transplant ward [10]. It should be noted that five of our patients—and four of the eight patients with isolated gut aspergillosis—habitually ate food that was extremely rich in spices.

Third, a major point is that four of the eight patients with isolated gut aspergillosis had a positive serum GM antigenaemia test finding; two of them (patients 3 and 6) had an index >4, with no evidence of respiratory lesion. Therefore, before a GM antigenaemia test finding is regarded as being false-positive, the possibility of gut aspergillosis should certainly be considered in at-risk patients presenting with abdominal symptoms. In the revised version of the EORTC-MSG criteria, there is no definition of probable gut aspergillosis [6]. Therefore, we selected only proven cases. Although it would be extremely difficult to establish a relationship between a positive serum GM antigenaemia test finding and gut symptoms in such immunocompromised patients, we would like to emphasize that the persistence of a positive GM antigenaemia test finding that is not explained by a lung or sinus lesion should lead to an exhaustive search for its origin, including a gut localization, before being considered to be false-positive. Taking in account an unexplained GM antigenaemia test finding is even more important if one considers the poor specificity of clinical symptoms and of imaging. The clinical significance of the presence of *Aspergillus* spp. in stool samples cannot be determined from our study.

Fourth, when serial GM antigenaemia tests were performed, we found a good relationship between the evolution of the GM antigenaemia test findings over time under

treatment and the final outcome, as in other localizations of aspergillosis [16,17]. Among the 16 patients who had a positive GM antigenaemia test finding at diagnosis, treatment led to a normalization in a mean time of 57 days (range: 7–160 days) in seven patients, and all but one were alive at 12 weeks. In contrast, the nine patients whose GM antigenaemia test findings remained positive under treatment for a mean time of 20 days (range: 2–79 days) died before the 12th week after diagnosis.

The optimal treatment and the respective contribution of surgery vs. antifungals cannot be clearly stated. Antifungals should certainly be administered, preferably intravenously. When surgery is decided on for diagnostic purposes, this is also a good opportunity to reduce the fungal burden, at the same time as dealing with other possible complications. The benefit of surgery to remove the gut lesion should logically be higher—perhaps curative—in isolated than in disseminated forms. When the diagnosis has already been made, surgery in the absence of severe complications (perforation and haemorrhage) should certainly be cautiously considered, especially in disseminated forms and when the patient is deeply neutropenic.

## Conclusion

The gut seems to be an exceptional site of *Aspergillus* infection in haematology patients. The diagnosis is extremely difficult in the absence of surgical investigation, owing to the poor specificity of the symptoms and the absence of characteristic imaging. The overall mortality rate was 57% in the patients of our series. Patients with a positive GM antigenaemia test finding that is unexplained by respiratory lesions should be suspected of having gut aspergillosis in the presence of abdominal symptoms. Diagnostic procedures should be performed without delay. Haematologists have to be aware of this complication, whose frequency may be underestimated. In most cases, it seems logical to combine medical and surgical therapy. However, the optimal therapy is so far not established.

## Acknowledgements

The authors are indebted to J. Tran-Vanhieu, Pathology Department, Henri Mondor University Hospital, who kindly provided the histological data of patient 4 presented in Fig. 2. They are also indebted to the physicians, nurses, data managers, microbiologists and pathologists of the participating centres.

## Authorship and Disclosures

E. Kazan and C. Cordonnier designed the study. E. Kazan collected the data. J. Maertens, R. Herbrecht, M. Weisser, B. Gachot, A. Vekhoff, D. Caillot, E. Raffoux, T. Fagot, O. Reman, F. Isnard, A. Thiebaut and C. Cordonnier provided data. E. Kazan, S. Bretagne and C. Cordonnier analysed the data. E. Kazan drafted the manuscript. All authors edited the manuscript and approved the final version.

## Transparency Declaration

All authors: no conflict of interest to declare.

## References

1. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood* 2002; 100: 4358–4366.
2. Hori A, Kami M, Kishi Y, Machida U, Matsumura T, Kashima T. Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. *J Hosp Infect* 2002; 50: 175–182.
3. Prescott RJ, Harris M, Banerjee SS. Fungal infections of the small and large intestine. *J Clin Pathol* 1992; 45: 806–811.
4. Davies S. *Aspergillosis in the immunocompromised patient*. Springfield, IL: Thomas, 1985.
5. Eggimann P, Chevrolet JC, Starobinski M *et al.* Primary invasive aspergillosis of the digestive tract: report of two cases and review of the literature. *Infection* 2006; 34: 333–338.
6. De Pauw B, Walsh T, Donnelly JP *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. *Clin Infect Dis* 2008; 46: 1813–1821.
7. Segal B, Herbrecht R, Stevens DA *et al.* Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; 47: 674–683.
8. Chambon-Pautas C, Costa JM, Chaumette MT, Cordonnier C, Bretagne S. Galactomannan and polymerase chain reaction for the diagnosis of primary digestive aspergillosis in a patient with acute myeloid leukaemia. *J Infect* 2001; 43: 213–214.
9. Elvira CRd. Med-AB Forms Manual: a guide to the completion of the EBMT HSCT Med-AB forms. Appendix iii. In EBMT registry: User guide to Promise 2.2, 23 September 2009; http://www.ebmt.org.
10. De Bock R, Gyssens I, Peetermans M, Nolard N. Aspergillus in pepper. *Lancet* 1989; 2: 331–332.
11. Boon AP, O'Brien D, Adams DH. 10 year review of invasive aspergillosis detected at necropsy. *J Clin Pathol* 1991; 44: 452–454.
12. Vogeser M, Haas A, Aust D, Ruckdeschel G. Postmortem analysis of invasive aspergillosis in a tertiary care hospital. *Eur J Clin Microbiol Infect Dis* 1997; 16: 1–6.
13. Vogeser M, Wanders A, Haas A, Ruckdeschel G. A four-year review of fatal aspergillosis. *Eur J Clin Microbiol Infect Dis* 1999; 18: 42–45.

14. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. *Rev Infect Dis* 1990; 12: 1147–1201.
15. Herbrecht R, Denning DW, Patterson TF *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.
16. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. *Blood* 2001; 97: 1604–1610.
17. Woods G, Miceli MH, Grazziutti ML, Zhao W, Barlogie B, Anaissie E. Serum Aspergillus galactomannan antigen values strongly correlate with outcome of invasive aspergillosis: a study of 56 patients with hematologic cancer. *Cancer* 2007; 110: 830–834.